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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,745	06/22/2006	Clifford David Jones	101319-1 US	1031

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
4161	

MAIL DATE	DELIVERY MODE
09/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,745	JONES ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,11 and 15-19* is/are pending in the application.

4a) Of the above claim(s) *15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8,10,11 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/12/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-8, 10-11, and 15-19 are currently pending. Claims 15-18 are withdrawn. Claims 9 and 12-14 are cancelled. Accordingly, claims 1-8, 10-11 and 19 are the subject of this Office Action. This is the first Office Action on the merits of the claims.

Information Disclosure Statement

2. All references have been considered.

Priority

3. The earliest effective filing date afforded the instantly claimed invention has been determined to be 12/20/2004 as to claims 1-8, 10-11 and 19.

4. Acknowledgment is made of Applicant's claim for foreign priority pursuant to 35 U.S.C. 119(a) and 365(b) based on prior applications filed in the UK on 07/29/2007 and 12/24/2003. The certified copies have been filed in parent Application No. PCT/GB04/05337, filed on 12/20/2004.

Election/Restrictions

Applicant's election of Group I, drawn to a compound of Formula I and compositions, in the reply filed on 08/21/2008 is acknowledged. Applicant further elected the compound of Example 22 wherein R^1, R^2, R^3 and R^4 are hydrogen; A is phenyl; n is 0; L is $-N(R^8)C(O)N(R^9)$ and R^8 and R^9 are hydrogen; B is oxazolyl; m is 1 and R^6 is t-butyl. Because applicant did not distinctly and specifically point out the

supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

5. The requirement is thus deemed proper and is therefore made FINAL.

6. The elected species read upon claims 1-8, 10-11 and 19.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

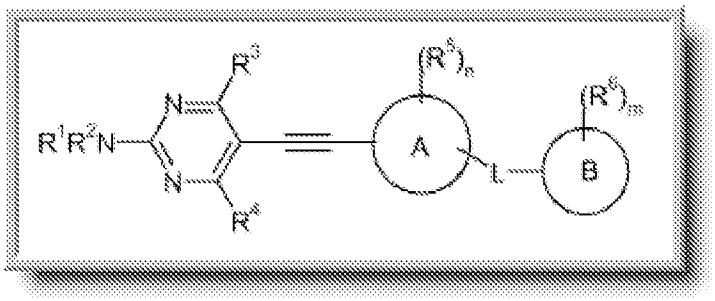
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

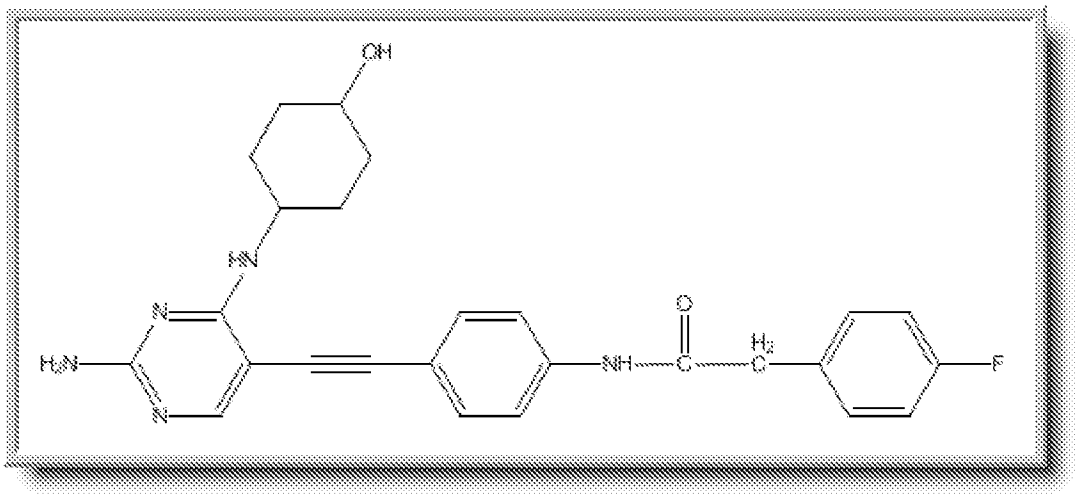
consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. **Claims 1-7, 11 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Beauchamp et al* (WO 02/08205)**.

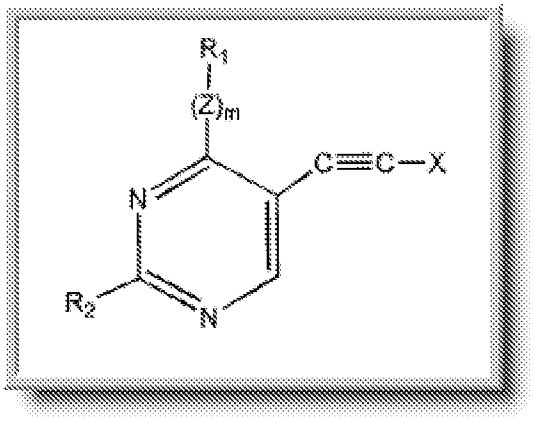
11. Instant claims 1-7, 11 and 19 are drawn to compounds of Formula I



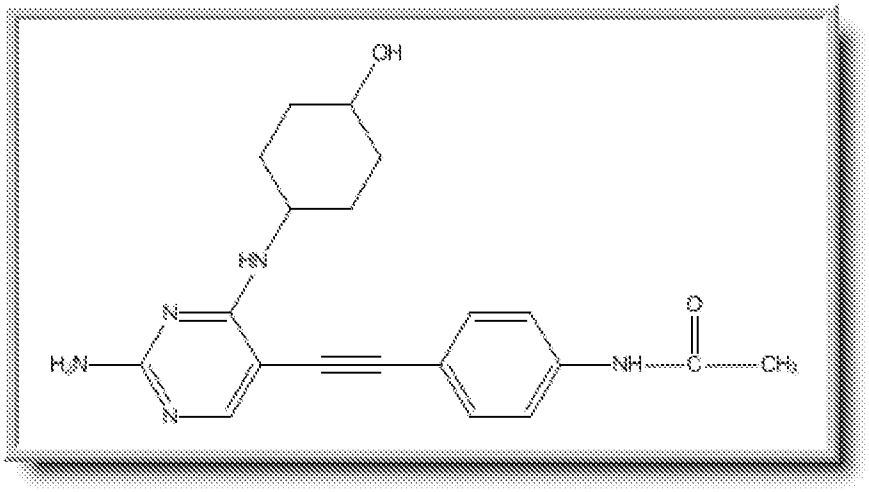
and compositions which are inhibitors of the Tie2 receptor tyrosine kinase, and which encompasses the following compound wherein R^1, R^2 and R^4 are hydrogen; R^3 represents the group NR^1R^2 wherein R^1 is hydrogen and R^2 is (3-6C)cycloalkyl$(CH_2)_x$ optionally substituted with hydroxy and, in which, x is 0; A is phenyl; n is 0; L is $-N(R^8)C(O)C(R^aR^b)$ wherein R^8, R^a and R^b are hydrogen; B is aryl (for example, phenyl); R^6 is halo (for example, fluoro); and m is 1:



12. *Beauchamp et al* teach compounds of Formula I



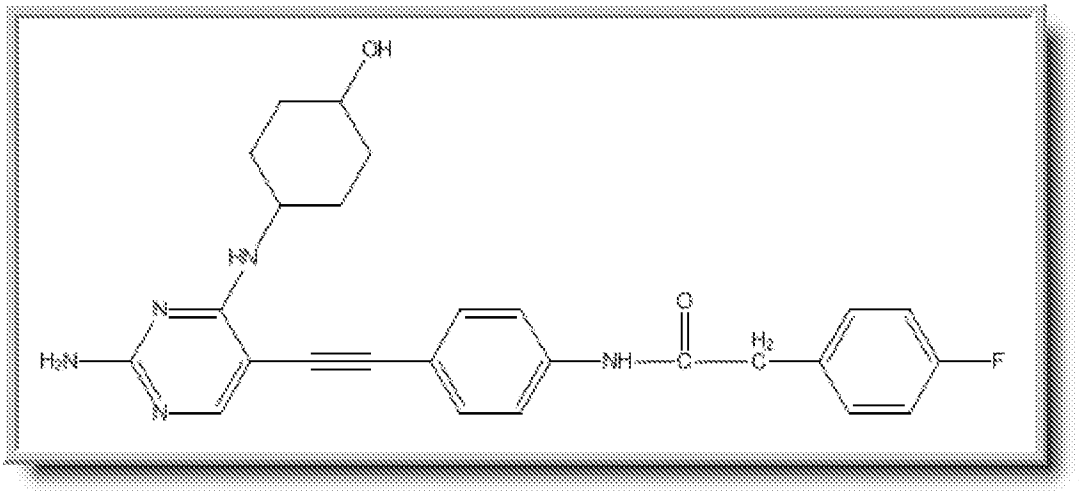
(Page 4, Lines 18-21) which are useful in the treatment of neurodegenerative disorders (Page 1, Line 4) and specifically disclose the following embodiment of Formula I



wherein Z is NH and m is 0; R_1 is (C2-6alkyl)$_a$(C3-10cycloalkyl)$_b$(C1-6alkyl)$_c$ wherein a and c are 0 and b is 1, optionally substituted with hydroxy; R_2 is NH_2; X is C6-10aryl (specifically phenyl) optionally substituted with (y); and (y) is NH-CO-R_4 wherein R_4 is C1-12 alkyl (specifically CH_3). Accordingly, the only difference between the compound of Formula I recited by the instant claims 1-7, 11 and 19 and the compound taught by *Beauchamp et al* is that (in *Beauchamp et al*) R_4 is CH_3 whereas the instant application is drawn to a

compound wherein the group corresponding to R_4 is (C1alkyl)aryl halogen. Significantly, *Beauchamp et al* teach only four possibilities for R_4; namely, H, C1-12alkyl, aryl or (C1-6alkyl)aryl halogen (Page 47, Lines 21-22). Thus, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to formulate the compound encompassed by instant claims 1-7, 11 and 19 in light of *Beauchamp et al* for the following reasons: **First**, *Beauchamp et al* specifically disclose a compound wherein X is phenyl substituted with NH-CO-R_4 and, furthermore, *Beauchamp et al* identify a finite and limited number of possibilities for R_4. A person of ordinary skill in the art at the time the invention was made would have pursued the finite and limited number of possible groups with predictable and reasonable success to formulate the compound encompassed by instant claims 1-7, 11 and 19. **Second**, one of ordinary skill in the art would have recognized, in light of *Beauchamp et al* – which teach four possible variations at R_4 – that each possible group is functionally equivalent, and the simple substitution of one known element for another to obtain predictable results would be obvious.

13. The fact that the instant compounds – including the compound represented by the following structure



which is encompassed by claims 1-7, 11 and 19 and which is obvious in view of *Beauchamp et al* – are alleged inhibitors of Tie2, whereas the compounds taught by *Beauchamp et al* are useful in the treatment of neurodegenerative disorders, is irrelevant. As discussed above, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to formulate the above compound in view of *Beauchamp et al* who teach structurally similar compounds having a limited number of possibilities at their only point of variation from the above compound. Accordingly, one of ordinary skill in the art would have been motivated to pursue each of the limited possibilities taught by *Beauchamp et al* to arrive at the above compound to obtain predictable results (predictable for the treatment of neurodegenerative disorders as taught by *Beauchamp et al*). Thus, the fact that the instant application alleges a distinct utility for the compounds and the possibility that the alleged utility may not have been a predictable result of the obvious modification is irrelevant since the instant claims are drawn only to the compounds themselves, and not the processes of using the compounds.

14. Instant claim 11 is drawn a pharmaceutical composition of Formula I in association with a pharmaceutically acceptable diluent or carrier. *Beauchamp et al* specifically teach "The formulations of the present invention comprise a compound of Formula I, as above defined... together with one or more pharmaceutically acceptable carriers therefor and optionally other therapeutic ingredients" (Page 14, Lines 23-24)

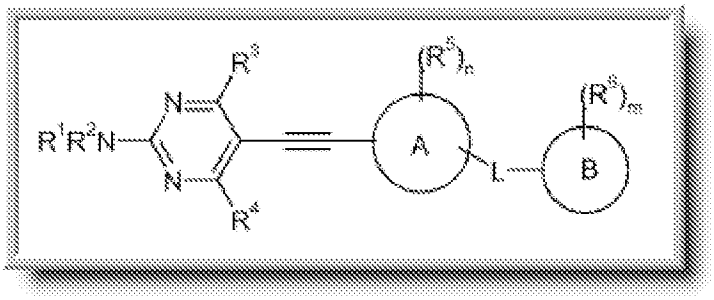
Claim Rejections - 35 USC § 112

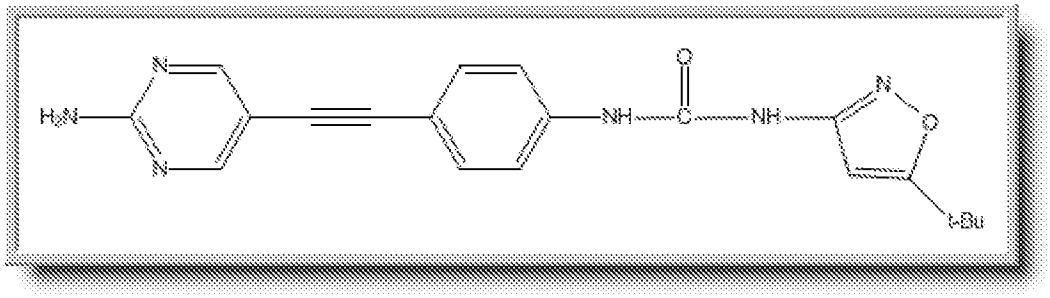
15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. **Claims 1-8, 10-11 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention**.

17. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered, with the most relevant factors discussed below.

18. Nature of the invention: Instant claims 1-8, 10-11 and 19 are drawn to compounds of Formula I  and compositions, including the elected specie

 (Example 22)

all of which are disclosed to be useful as inhibitors of the Tie2 receptor tyrosine kinase. The development of inhibitors is complex. This is especially true in the case of Tie2 inhibitors since, as evidenced by *Augustin HG* (Brit J Radiol 76:S3-S10, 2003), the biology of the Tie2 system is poorly understood (Page S5, Column 1, Paragraph 3). Indeed, despite a recognized need for inhibitors of Tie2 "there are only a few such compounds" (*Mazitschek and Giannis*, Curr Op Chem Biol, 8:432-441, 2004)(Page 435, Column 2, Paragraph 4). Accordingly, the nature of the invention is one of extreme complexity.

19. Breadth of the claims: The claims are drawn to compound of Formula I which, given the numerous variable groups and the numerous possibilities of each variable, encompasses literally thousands of compounds. Accordingly, the breadth claims

exacerbates the complexity of the invention in that it requires each of the thousands of compounds (including the elected compound) which are encompassed by the generic Formula I to be capable of inhibiting Tie2 kinase.

20. Guidance of the specification/The existence of working examples: Applicant provides *in vitro* data that three (Examples 19, 33 and 48) of the thousands of compounds encompassed by the invention inhibit Tie2 kinase and inhibit autophosphorylation of Tie2 kinase (Page 85 of the Specification, Table A). It is notable that no information is provided as to the activity of the elected specie, Example 22.

21. State of the art/Predictability of the art: As discussed above, the nature of the invention is complex and, despite a recognized need for inhibitors of Tie2, there are few available. Moreover, among the Tie2 inhibitors that have been developed, it is clear that minor structural changes can have significant impacts on their activity. As evidenced by *Stahl et al* (Angewandte Chemie Int Ed 41:1174-1178, 2002) SAR studies demonstrated that changes to compound structure altered Tie2 inhibitory activity by more than 3-fold (Page 1176, Table 1). Similarly, *Miyazaki et al* (Bioorgan Med Chem Lett 17:250-254, 2007) reported over 100-fold changes in Tie2 inhibitory activity between related compounds having a single modification (Page 252, Table 3). Significantly, the inhibitory activity of the three tested compounds in the instant application varied drastically (Page 85 of the Specification, Table A). Accordingly, it is highly unpredictable whether structurally related compounds will possess Tie2 inhibitory activity. More specifically, it is highly unpredictable whether Applicant's elected specie, Example 22, will possess Tie2 inhibitory activity.

22. Amount of experimentation necessary: Given the complex nature of the invention, which is exacerbated by the enormous breadth of the claims, given the limited number of working examples – and especially considering that no working examples are provided regarding the elected specie, and furthermore given the unpredictability in the art, one of ordinary skill in the art would be required to undertake undue experimentation (ie, make each of the thousands of compounds encompassed by the claims and then determine on a case by case basis which of those compounds possess Tie2 inhibitory activity) in order to practice the invention. As such, the elected specie is not enabled for inhibiting Tie2 activity. Accordingly, claims 1-8, 10-11 and 19 are rejected.

Double Patenting

23. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

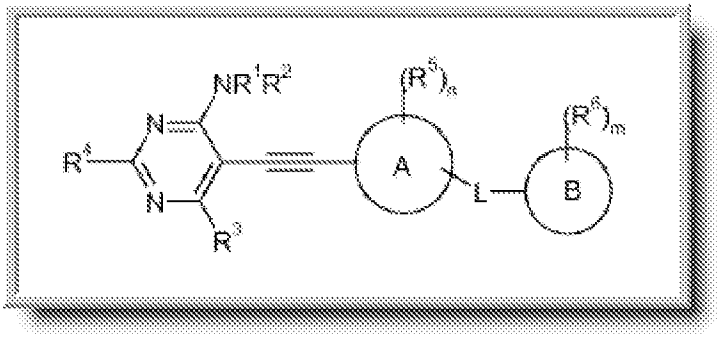
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

24. **Claims 1-8, 10-11 and 19 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 10/596,740.**

This is a provisional obviousness-type double patenting rejection.

The '740 application is drawn to compounds of Formula I



having Tie2 inhibitory activity wherein the variables are defined in the claims. Notably, there is significant overlap between the variables as defined in the '740 application and as defined in the instant

application. Accordingly, the compounds of the '740 application are structurally and functionally similar to the compounds of the instant application with the only difference being the location of the NR^1R^2 and the R^4 groups on the pyrimidine ring. As stated by MPEP 2144.09:

> A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979).

and furthermore,

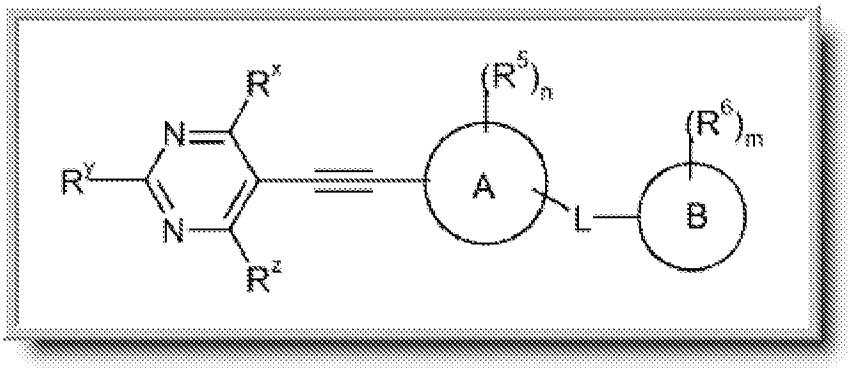
> Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by $-CH_2-$ groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

In the instant case, the compounds are structurally and functionally similar, differing only in the exchange of variable groups located on the pyrimidine ring of the compound and, when viewed as a whole, it would have been prima facie obvious for a person of ordinary skill in the art at the time the invention was made to exchange the positions of the two variable groups on the pyrimidine ring to obtain the expected results.

25. **Claims 1-8, 10-11 and 19 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 7-11 of copending Application No. 11/815,182.**

This is a provisional obviousness-type double patenting rejection.

26. The '182 application is drawn to compounds of Formula I

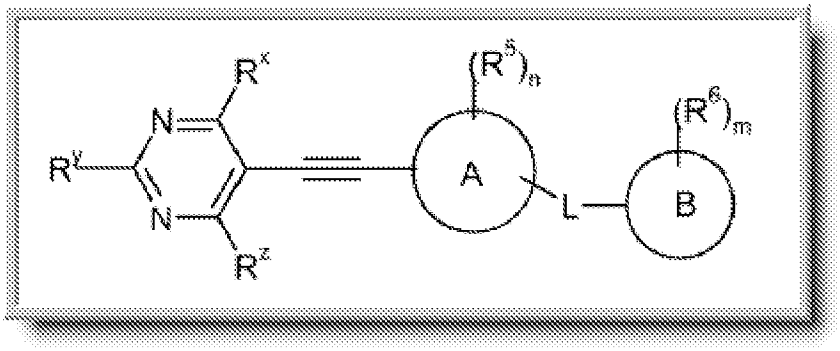


having Tie2 inhibitory activity wherein the variable groups are as defined in the claims. Notably, there is significant overlap between the variables as defined in the '182 application and as defined in the instant application. Moreover, the claims of each application encompass compound species that overlap the claims of the other invention.

27. **Claims 1-8, 10-11 and 19 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 7-11 of copending Application No. 11/815,269.**

This is a provisional obviousness-type double patenting rejection.

28. The '269 application is drawn to compounds of Formula I



having Tie2 inhibitory activity wherein the variable groups are as defined in the claims. Notably, there is significant overlap between the variables as defined in the '269 application and as defined in the instant application. Moreover, the claims of each application encompass compound species that overlap the claims of the other invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571)270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on (571) 272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 4161

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4161